Monoarticular Arthropathy

Introduction

This lesson is titled *Monoarticular Arthropathy* because the diseases contained within typically present in one joint at a time. That is not to say that any of these diseases, over time, could not happen in multiple joints. It is to say that when encountering a single red, hot, swollen, tender, and inflamed joint, you should rapidly consider one of these diseases. There are two main categories. The first is **crystal deposition** (gout and pseudogout). The second is **septic arthritis** (*Staph. aureus* and *Neisseria gonorrhoeae*). We go through gout in detail, then use it to simplify pseudogout. We then go through *Staph. aureus* septic arthritis in detail, using it to simplify *Neisseria gonorrhoeae* septic arthritis.

Crystal Disease—Gout

Gout is a crystal deposition disease. Crystals precipitate out into the joint space and are attacked by inflammatory cells. In gout, the crystals are **monosodium urate crystal—**a precipitation of crystals made from uric acid and monosodium. Not surprisingly, then, the strongest risk factor for the formation of monosodium urate crystals is **hyperuricemia**, too much (hyper) uric acid (-uric-) in the blood (-emia). Primary causes of hyperuricemia are from inborn errors of metabolism that involve purine biotransformation, such as Lesch-Nyhan syndrome. Secondary causes of hyperuricemia are vastly more common, and occur in two general mechanisms—underexcretion and overproduction. **Underexcretion** of uric acid in the kidneys accounts for 90% of hyperuricemia cases. Genetics determine uric acid secretion. Uric acid is secreted by the kidneys. Some humans have more excretion, some have less. People with less have a higher uric acid level, are more prone to gout, and are more susceptible to gout flares. **Overproduction** of uric acid occurs with increased cell turnover, as in leukemia.

Most patients who have hyperuricemia have no reversible cause—they are genetic underexcreters (irreversible risk factor). But there are other risk factors for gout beyond just hyperuricemia. Those are being male (also irreversible risk factor), and having hypertension, diabetes, dyslipidemia, and obesity.

Patients with hyperuricemia are kept in balance most of the time. The rates of crystal deposition, resorption, precipitation, and dissolution are kept in equilibrium. When that equilibrium is compromised, acute gout attacks, called gout flares, can occur.

Gout flares are **acute inflammatory** reactions to excess precipitation of crystals into joints. Flares are precipitated by **food rich in purines**, such as red meat and seafood (increases in purine metabolism lead to an increase in uric concentration), and **alcohol intake** (EtOH metabolites and uric acid compete for secretion sites in the nephron), but also by **trauma**. Purines and alcohol can cause a flare in any joint. Trauma causes a flare in the joint that was traumatized. Just a simple stubbed toe or a banged knee can set off the flare. Gout flares present with **monoarticular** joint swelling that is **intensely inflammatory**. That means there is going to be pain, erythema, loss of function, and tenderness. Classically, the first knuckle of the big toe (metatarsophalangeal joint) gets inflamed, a condition called **podagra**. Patients will not tolerate any physical contact, as it is intensely painful. In clinical medicine, a history of gout and an inflamed joint are enough to make the diagnosis and initiate treatment. In the basic sciences, however, the focus will not be on diagnosis or management, but will focus on obtaining an arthrocentesis and interpreting the results. As a general rule, if ever you encounter an overtly inflamed joint, you will tap it. More on that in a bit.

Chronic gouty arthritis, also called **tophaceous gout**, is characterized by tophi—collections of densely packed urate crystals that deposit into soft tissues and joints. Classic locations are on the external ear, the olecranon bursa, or the Achilles tendon, though they may deposit in any joint or any soft tissue. The tophi themselves are lumps seen through the skin over the joints. If you open them surgically, or if the

skin breaks over the lesions, what lies beneath is a chalky white paste—the crystals. When they deposit into joints, they can cause an erosive arthritis. **Erosions** occur in the **bone** at the joint space. Tophi are radiolucent on X-ray. Tophi occupy space, and so can wedge their way into the bones of the joint, resulting in the erosion of the bones of that joint. What you see is a divot in the bone, the periosteum intact, but as if there were a punch biopsy that removed a piece at the edge. This results in **punched-out** lesions and **overhanging edges** where the normal remaining bone appears to be covering the punched-out lesion (see Figure 1.2).

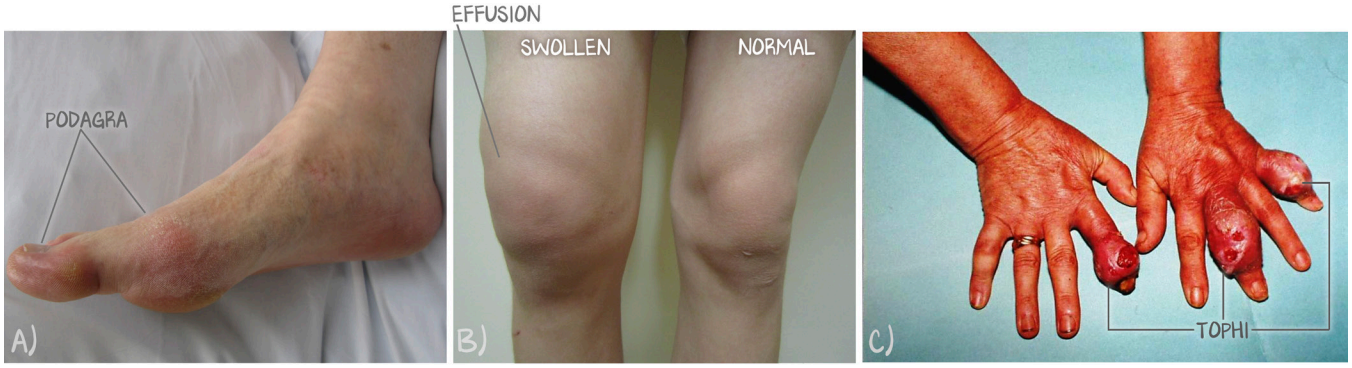


Figure 1.1: Presentations of Gout
(a) Podagra—the inflamed, red toe—is the classic presentation of acute gout attacks. (b) It only matters which joint receives trauma; that joint can then become inflamed. A joint effusion—the knee, in this case—demonstrates that large joints can be affected as well as small joints. (c) Rare in the developed world, chronic tophaceous gout is an accumulation of uric acid crystals beneath the skin.

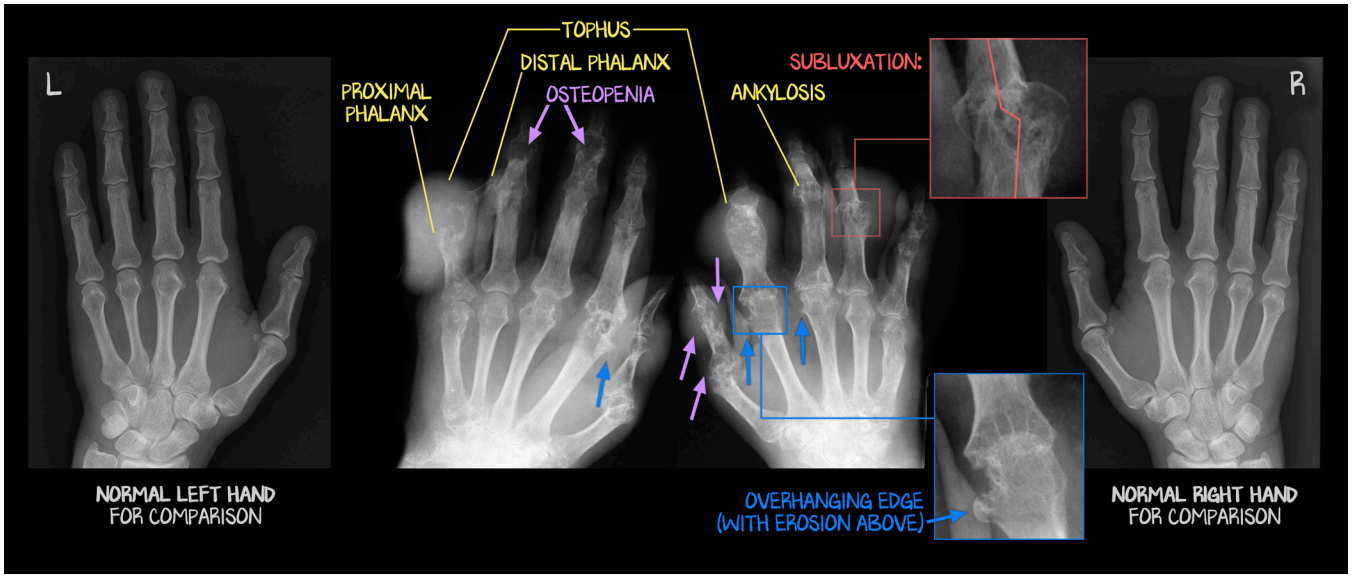
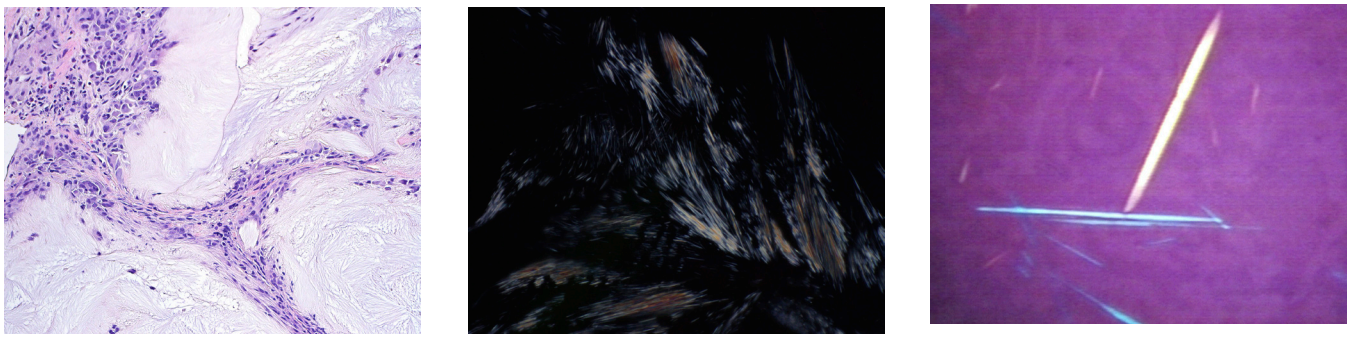


Figure 1.2: Gouty Radiographs
Gout need not get this severe. However, if not treated, gout crystals can accumulate and destroy joints. Gout classically has erosions into the proximal phalange, which is sometimes referred to as "punched out with an overhanging edge." Several of those lesions are visible on the hands in the center panel. The thumbs have erosions and severe osteopenia (marked with *). The halos of white around the bones represent the tophi, the crystals under the soft tissue. The pathology is flanked by normal left and right hands for comparison.

The diagnosis is confirmed with **arthrocentesis**—drainage of the knee and evaluation of crystals under the microscope. The gout crystals are **needle-shaped** (long, thin lines) and are **strongly** (all the crystals will be lit up) **negatively birefringent** under polarized light. This means the slide is a multicolored array of blues, yellows, and greens, and each one is a sliver of light. Gout is one color (blue) if perpendicular, and another color (yellow) if parallel. Negatively birefringent means yellow in parallel light. Focus on "needle-shaped" and "all the crystals are illuminated."



(a) (b) (c)

Figure 1.3: Gout Biopsies
(a) By regular (non-polarized) light microscopy examination, a tissue biopsy of gout shows large pale acellular aggregates of urate crystals surrounded by a rim of reactive histiocytes and giant cells (the purple cells). (b) The monosodium urate crystals of gout are needle shaped and birefringent under polarized light examination. They take on a yellow color or blue color depending on their orientation to the polarized light. (c) Thin, needle-shaped crystals appear blue or yellow depending on their orientation.

The treatment for gout is complex, and deciding between agents will not be the focus of the preclinical sciences. The pharmacology on gout-related treatments will dive into the mechanisms and how both diet/lifestyle and pharmacology are related to the process of purine metabolism and uric acid secretion.

Crystal Disease—Pseudogout

Pseudogout is the crystal deposition disease of the **elderly**. Pseudogout crystal deposition is of **calcium pyrophosphate**. Pseudogout has no association with purine metabolism, uric acid, or food consumption. Men and women are affected equally. The only risk factor is being old, though commonly tested associations are with **hemochromatosis** and **hyperparathyroidism**. Hypercalcemia without hyperparathyroidism is not a risk factor.

Acute pseudogout looks like a **gout flare**. Both the presentation and treatment are the same for gout and pseudogout, except that pseudogout classically targets the **knee**. During an acute attack, an arthrocentesis shows **crystals** that are **rhomboid** in shape and that are **weakly positively birefringent to polarized light**. "Weakly" means, "not every crystal on the slide is illuminated," and "positively birefringent to polarized light" means, "the ones that are illuminated are blue." Positive birefringence is blue in parallel light.

Chronic pseudogout looks like **osteoarthritis**. Repeated flares lead to joint-space narrowing and **chondrocalcinosis** (chondro: cartilage; calcinosis: calcification) secondary to linear deposits of crystals in articular cartilage. Pseudogout classically targets the knee. Seeing "the knee" and "joint-space narrowing" calls to mind the classic illness script for osteoarthritis. To separate osteoarthritis and chronic pseudogout on an X-ray, look for chondrocalcinosis; by history, look for repeated flares.

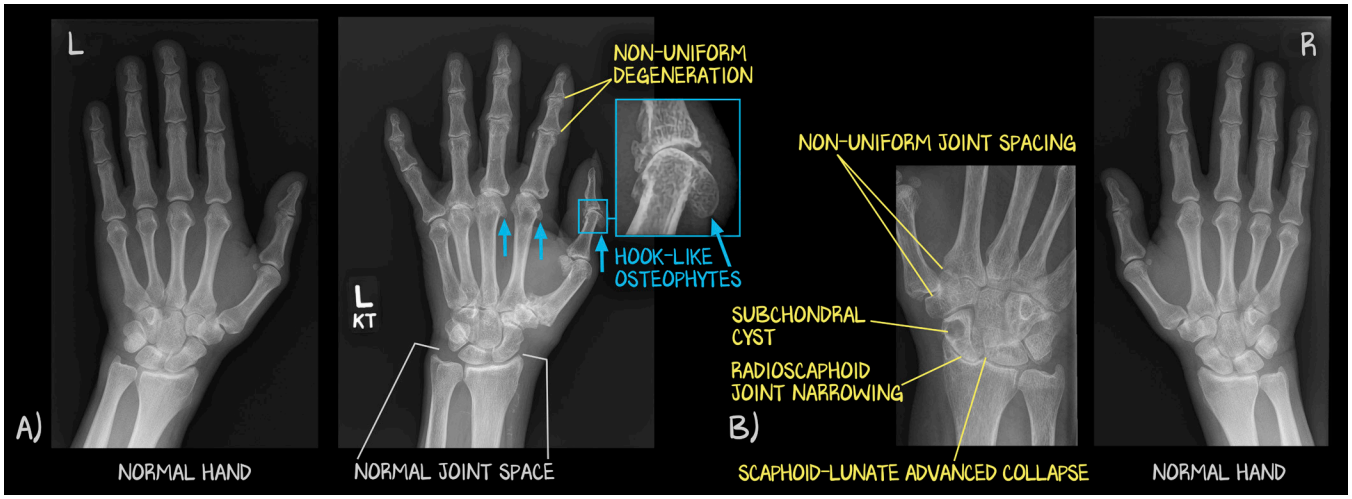


Figure 1.4: Hands with Calcium Pyrophosphate Deposition Disease (CPPD)
CPPD classically causes hook-like osteophytes and scapholunate advanced collapse (SLAC wrist). The destruction of joints is non-uniform and asymmetrical. (A) A normal left hand is shown for comparison with the affected hand. Degeneration of the first digit DIP and PIP and several hook-like osteophytes (arrows) are present, but the wrist is normal. This patient does have CPPD, but the diagnosis could not be made from this film alone. (B) A normal right-hand x-ray is shown for comparison with the affected hand, which is magnified so you can see the changed angles. A subchondral cyst, radioscaphoid joint narrowing, and SLAC wrist are present.

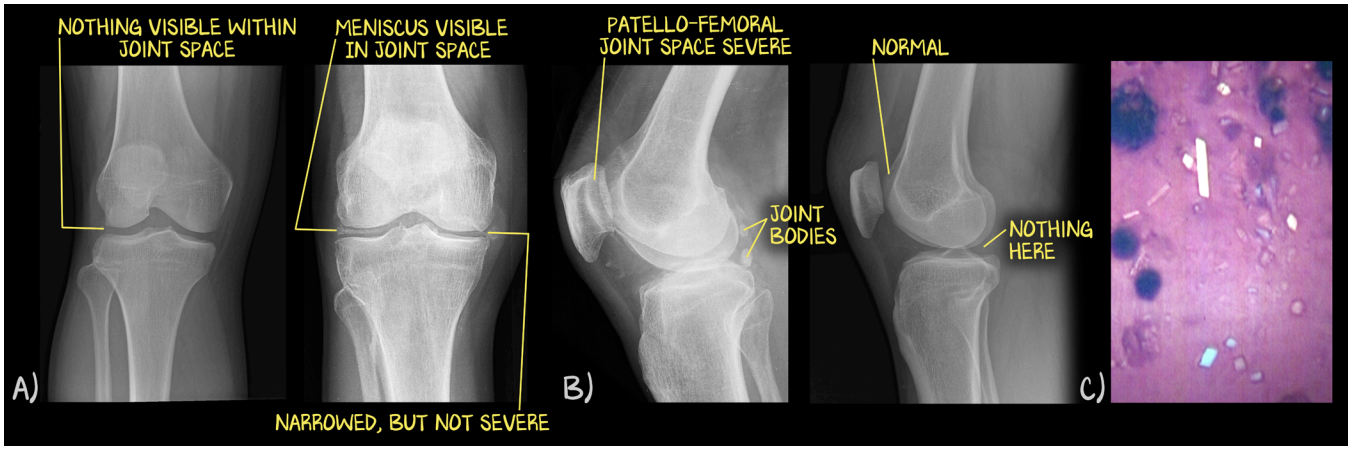


Figure 1.5: Knees with Calcium Pyrophosphate Deposition Disease (CPPD) and Crystals
CPPD typically spares the medial and lateral compartments but severely affects the patellofemoral joint space. Chondrocalcinosis is the deposition of calcium in chondrocytes, making the menisci and bursae visible on x-ray (a) Normal knee compared to an affected knee. The meniscus is visible between the femur and the tibia in the affected knee but is not visible in the normal knee. Also note that there is some loss of the medial and lateral joint spaces, as this person also has osteoarthritis. (b) Normal and diseased lateral films demonstrate the severe loss of the patellofemoral joint space. Joint bodies (sometimes called loose bodies), indicative of osteoarthritis, are also present. (c) The calcium pyrophosphate crystals of pseudogout are rhomboid-shaped and negatively birefringent under polarized light examination.

DISEASE	RISK FACTORS	PRESENTATION	X-RAY	BIOPSY
Gout (urate crystals)	Male, HTN, obesity, HLD, purine diet	Big toe, podagra Tophaceous gout	Erosions Punch lesions Overhanging edge	Negatively birefringent needle-shaped crystals
Pseudogout (calcium crystals)	Advanced age, hyperparathyroidism	Knee Acute or chronic	Chondrocalcinosis Joint space narrowing	Weakly positively birefringent crystals Rhomboid-shaped

Table 1.1: Comparison of Crystal Deposition Disease
They differ in everything except "are crystals" and "can have an acute flare."

	NORMAL	OSTEOARTHRITIS	INFLAMMATORY	SEPTIC
Color	Clear	Clear	Cloudy	Opaque
WBC	< 2,000	< 2,000	2,000–20,000	> 50,000 (100,000)
Neutrophils	< 25%	< 25%	> 50%	> 75% (99%)

Table 1.2: Interpretation of Synovial Fluid
The evaluation of a synovial fluid arthrocentesis comes down to the WBC count and percentage of neutrophils. The appearance matches just how many white cells there are, unless it is actually a hemarthrosis, in which case this discussion is unnecessary. A noninflammatory effusion is, like a normal joint, not worth tapping because there isn't enough fluid. If tapped, there would be few cells (< 2,000 WBCs and they wouldn't be neutrophils). The true value of an arthrocentesis is to separate "shouldn't have tapped it" (normal and noninflammatory) from "ZOMFG SEPTIC JOINT!" leaving "non-infectious inflammation" in the part left over. If there are > 50,000 WBC, it is septic, period. The presence of more white cells than that, and a neutrophilic predominance approaching 100%, are helpful, but the 50,000 number is a done-deal cut-off. If there are < 2,000 WBC and few are neutrophils, it is neither septic nor inflammatory. Anything between 2,000 and 20,000 is inflammatory, inflammatory meaning any inflammation of any kind other than infection. The range of 20,000 to 50,000 is too ambiguous, so you can safely ignore that range for now.

Septic Arthritis

Septic arthritis is a **joint inflammation** (arthritis) caused by a **bacterial infection** (septic). Septic arthritis most often occurs via **hematogenous seeding** of the joint. Of course, a penetrating wound through skin and into a joint space can inoculate that joint space, but when that happens, a washout is performed in the operating room to prevent the septic arthritis. It is not a diagnostic conundrum. The clinical consideration will come from a joint that is infected with the skin above it still intact. What you should look for is a joint replacement (infected surgery) or hematogenous spread without trauma. The people who get septic arthritis are those who have risk factors. One is **doing something that gets your blood infected—**intravenous drug abuse for *Staph. aureus*, unprotected sex for *Neisseria gonorrhoeae*. Two is having **joints that are ready to be seeded—**pre-existing joint disease (gout, pseudogout, osteoarthritis, rheumatoid arthritis, prosthetics).

The patient will present with an **extremely toxic joint**. Toxic means overt inflammatory symptoms—**fever, leukocytosis,** tachycardia. The joint itself will also be acute and toxic—**red, hot, swollen, tender** joint with loss of mobility. There may also be overlying erythema or cellulitis of the skin above the joint. The diagnosis is confirmed with an **arthrocentesis**. If you see a red, hot, swollen joint that has fluctuance, even if you know for sure it is gout, you will perform an arthrocentesis at your level of training. If the **WBC are greater than 50,000** in the synovial fluid, it is a septic joint. Those WBCs will be **exclusively neutrophils**.

The diagnosis of a septic joint is a surgical emergency. Sepsis is treated initially with volume resuscitation and antibiotics, but the treatment of choice is an emergent washout. As the causative agent is most often *Staph. aureus*, treatment begins with **vancomycin**. A Gram stain and culture of the arthrocentesis fluid, or the washout fluid, will yield the causative organism. Any prosthetic must be removed.

Gonococcal Septic Arthritis

Any bacteria can infect a joint, and the culture of the synovial fluid will tell you what organism it is after the septic joint has been managed. We want you learning there are two empiric considerations for septic arthritis: staph (*Staph. aureus*) and non-staph (*Neisseria gonorrhoeae*). Gonococcal septic arthritis is a form of septic arthritis and is by **hematogenous spread** only—it is hard to directly inoculate a joint with *Neisseria*. This means, by definition, disseminated gonorrhea. The patient will have contracted *Neisseria gonorrhoeae* as an STI, left it untreated, and then developed the septic joint. If you have a septic joint (> 50,000 WBC on synovial fluid) and no organisms seen on Gram stain, consider gonorrhea. The diagnosis is made with **synovial fluid NAAT** or **culture on Thayer-Martin agar** (this agar must be specified and is not routine). If *Neisseria gonorrhoeae* is suspected but the culture is negative, usual sites of transmission can be assessed with a NAAT—take samples from the throat, vagina, urethra, and anus. The treatment is with **ceftriaxone + azithromycin**.

* 280+ Test Prep

Disseminated gonorrhea (not the seronegative spondylarthritis associated with gonorrhea) may also present with **tenosynovitis**, **pustular dermatitis**, and **polyarthritis** with systemic symptoms. This presentation is often also seen without a history of the STI. This presents like many systemic autoimmune diseases and so while it is a presentation that may be seen, it is unlikely to appear this way on a licensure examination. However, if you get a question about gonorrhea septic arthritis and none of the risk factors are there, look for this triad.

Citations

Figures 1.1a, 1.1b, 1.3: Courtesy of Jerad M. Gardner, MD. https://www.youtube.com/user/JeradMGardnerMD

